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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,536	05/24/2001	Peter D. Gluckman	37522-1002P2	4791

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EXAMINER
CELSA, BENNETT M

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary

Application No.	Applicant(s)
09/866,536	Gluckman et al.
Examiner	**Art Unit**
Bennett Celsa	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892) ✓
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) ✓ ✓
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4-6*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

Claims 1-7 are currently pending.

1. Applicant's election without traverse of GPE in Paper No. 10 (mailed 3/13/03) which reads on claims 1-7 is acknowledged.

Priority

2. The present application is a CIP of 08/907,918 (filed 8/11/97). Applicant's claim for priority under 35 U.S.C. 120 is acknowledged. However, the 08/907,918 application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-7 of this application. For example, the prior application fails to provide descriptive and enabling support for treatment or prophylaxis of "the functional symptoms of Parkinsons disease" (e.g. "involving dopaminergic neurons") ; GPE analog or mimetic etc. Accordingly, the presently claimed invention is accorded the present filing date (e.g. 5/24/2001) for purposes of prior art

Claim Rejections - 35 USC § 112

3.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1 (and claims dependent thereon), the phrase "the functional symptoms of Parkinson's disease" lacks clear antecedent basis.

B. In claim 1(and claims dependent thereon), use of the term "prophylaxis" is confusing in the presently claimed context regarding "a patient suffering from the functional symptoms of Parkinson's disease"; to the extent that "prophylaxis" is synonymous with prevention , which implies a host who is disease or symptom free. To the extent "prophylaxis" does not encompass prevention it is confusing as to how this term distinguishes from "treatment" as already claimed.

C. In claim 1 (and claims dependent thereon) use of the term "the functional symptoms of Parkinson's disease" is confusing as to the metes and bounds of this term and how "the functional symptoms" differ from "non-functional symptoms" of the same disease state.

D. In claim 1 (and claims dependent thereon", use of the term "GPE" is confusing as to whether this term refers to Glu-Pro-Glu (e.g. see specification page 3, lines 9-15; page 7, lines 1-10) or includes additional dipeptides or other peptides (e.g.see specification page 9, especially lines 23-28) .

E. In claim 1 (and claims dependent thereon), the metes and bounds of the terms "analog (of GPE)" ; "mimetic(of GPE)" or "prodrug" (of GPE) is confusing for several reasons. First, as described in item D. above the specification giver to different definitions of GPE (e.g. specification pages 3 and 7 vs. Specification page 9). Accordingly, in order to determine an "analog"/ "mimetic"/"prodrug" of GPE one must first understand the metes and bounds of GPE. The specification fails to provide a single definition of the terms "mimetic" or "prodrug" or even

describe a single compound which is exemplary thereof. Regarding the term "analog", the specification (e.g pages 9-11) appear to define "analog" (of GPE) in two ways:

I. as "compounds which exert a similar biological effect to GPE" or

II. "compounds which increase the active concentration of GPE and/or naturally occurring analogues thereof in the CNS" wherein the "active concentration" refers to a concentration which is "able to exert an effect on CNS damage"; in which only IGF-1 is exemplified.

Regarding the first definition , failure to define "the biological effect" and the degree of similarity necessary to qualify as "an analog of GPE" renders the first definition indefinite.

Regarding, the second definition, failure to recite the degree of GPE concentration and/or means of measure thereof; and the failure to describe "naturally occurring analogues of GPE within the second definition renders, the second definition indefinite.

F. Method claims 1-2,4-7 are incomplete since no method step is recited.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (LACK OF WRITTEN DESCRIPTION).

Claims 1-7 describe the use of Gly-Pro-Glu **"analogs/ mimetics/prodrugs "** for use in treatment or prophylaxis of a patient suffering from the functional symptoms of Parki*nsons disease* . However, the metes and bounds of compounds encompassing this terminology is unclear. First, the specification provides different definitions of GPE (e.g. specification pages 3 and 7 vs. Specification page 9). Accordingly, in order to determine an "analog" /"mimetic"/ "prodrug" of GPE one must first understand the metes and bounds of GPE. Additionally, the specification fails to provide a single definition of the terms "mimetic" or "prodrug" of GPE; not describe a single compound which is exemplary thereof. Regarding the term "analog", the specification (e.g pages 9-11) appear to define "analog" (of GPE) in two ways:

I. as "compounds which exert a similar biological effect to GPE" or

II. "compounds which increase the active concentration of GPE and/or naturally occurring analogues thereof in the CNS" wherein the "active concentration" refers to a concentration which is "able to exert an effect on CNS damage"; in which only IGF-1 is exemplified.

Regarding the first definition , failure to define "the biological effect" and the degree of similarity necessary to qualify as "an analog of GPE" renders the first definition indefinite.

Regarding, the second definition, failure to recite the degree of GPE concentration and/or means of measure thereof; and the failure to describe "naturally occurring analogues of GPE within the second definition renders, the second definition indefinite.

Thus, the claimed invention encompasses an untold number of different compounds of different structure (e.g. potential deletion/substitution/addition or other alteration of a starting

structure) which need not share any decipherable common core structure relative to the reference compound (Glu-Pro-Gly).

In support of these claimed analogs/mimics the specification defines IGF-1 as being a Gly-Pro-Glu an analog and perhaps "Gly-Pro" or "Pro-Glu" (e.g. see one of the specification description of the term "GPE" as differing from Gly-Pro-GLu as described elsewhere as referring to GPE).

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Although directed to DNA compounds, this holding would be deemed to be applicable to a generic of compounds; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the compound or generic(s). For example, in a recent court case in line with *Eli Lilly, Judge Lourie writing for the CAFC* made the following observation:

> "A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) having the function of lessening inflammation of tissues, fails to distinguish any steroid from others having the same activity or function. Similarly, the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity. "

See: J. Lourie decision in *Enzo Biochem, Inc. v. Gen-Probe Inc. et al.* No. 01-1230 (CAFC: Decided April 2, 2002) (citation forthcoming).

In this regard, applicant is referred to the seminal case of *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and the "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

It is noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.*

As pointed out above, the specification discloses only limited examples that are neither representative of the claimed "analogs"/ "mimetic"/ "prodrug" of GPE (as referred to in the specification under its various definitions).

7. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a method of protecting dopaminergic neurons against death resulting from Parkinson's disease using a neuroprotective amount of Gly-Pro-Glu as described in the examples; the specification does not reasonably provide enablement for the scope of analogs/mimetics/prodrugs of Gly-Pro-Glu to treat all "functional symptoms of Parkinsons disease" as presently claimed. The specification does not enable nor provide sufficient description, for any person skilled in the art to which it pertains; or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims.

2. The nature of the invention

3. The state of the prior art;

4. The level of one of ordinary skill

5. The level of predictability in the art;

6. The amount of direction provided by the inventor;

7. The presence or absence of working examples;

8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure;

See :*In re Wands* USPQ 2d 1400 (CAFC 1988):

(1-2) The breadth of the claims and the nature of the invention:

Claims 1-7 describe the use of Gly-Pro-Glu **"analogs/ mimetics/prodrugs "** for use in treatment or prophylaxis of a patient suffering from the functional symptoms of Parki*nsons disease* . However, the metes and bounds of compounds encompassing this terminology is unclear. First, the specification provides different definitions of GPE (e.g. specification pages 3 and 7 vs. Specification page 9). Accordingly, in order to determine an "analog" /"mimetic"/ "prodrug" of GPE one must first understand the metes and bounds of GPE. Additionally, the specification fails to provide a single definition of the terms "mimetic" or "prodrug" of GPE; not describe a single compound which is exemplary thereof. Regarding the term "analog", the specification (e.g pages 9-11) appear to define "analog" (of GPE) in two ways:

I. as "compounds which exert a similar biological effect to GPE" or

II. "compounds which increase the active concentration of GPE and/or naturally occurring analogues thereof in the CNS" wherein the "active concentration" refers to a concentration which is "able to exert an effect on CNS damage"; in which only IGF-1 is exemplified.

Regarding the first definition , failure to define "the biological effect" and the degree of similarity necessary to qualify as "an analog of GPE" renders the first definition indefinite.

Regarding, the second definition, failure to recite the degree of GPE concentration and/or means of measure thereof; and the failure to describe "naturally occurring analogues of GPE within the second definition renders, the second definition indefinite.

Thus, the claimed invention encompasses an untold number of different compounds of different structure (e.g. potential deletion/substitution/addition or other alteration of a starting structure) which need not share any decipherable common core structure relative to the reference compound (Glu-Pro-Gly).

3 and 5) *The state of the prior art and the level of predictability in the art:*

In accordance with the present invention, the ability of a ligand (e.g. a hormone) to predictably bind a receptor is a prerequisite for obtaining "biological activity". However, ligand/receptor binding is stereospecific (e.g conformationally sensitive).(see Rudinger, Peptide Hormones (June 1976: J Parsons editor) pages 1-6; e.g. see page 4; and accordingly, the efficacy of binding of a ligand (e.g. cyclopentapeptide) to a receptor (e.g. enzyme/hormone etc.) to achieve physiological action is determined by the conformation of the given ligand. Thus the different aspects of biological activity cannot be predicted *a priori* but must be determined on a case to case base through experimental study. The careful design of synthetic analogues and their evaluation in biological systems which permit separate analysis of the various phases of receptor (e.g hormone) action is the best way of obtaining such information. See Rudinger, Peptide Hormones, (June 1976) (J.A. Parsons, editor) 1,5-6.

Further, Applicants are reminded that claims drawn to pharmaceutical use (e.g. the making of biologically active peptides) generally require supporting data which is both commensurate in scope and extrapolatable to human efficacy in view of the unpredictability in biological responses of pharmaceutical treatments. For the efficacy of a drug treatment in vivo faces unfavorable obstacles not present in vitro. For example, drug delivery to the targeted area must survive the acidic environment of the stomach if administered orally. Additionally, the drug if indeed immunogenic as many drugs are, must survive an antibody response which may act to deactivate the drug before it achieves its situs or desired response. For the delivery of the drugs to and/or across necessary cell surfaces in amounts needed to be efficacious, but not lethal to the organism, necessitates sensitive testing in order to adequately determine the proper human dosage.

(4) *The level of one of ordinary skill in the art:*

The level of skill would be high, most likely at the Ph.D. level.

(6-7) *The amount of direction provided by the inventor and the existence of working examples.*

The specification only provides support (e.g. examples) for using Gly-Pro-Glu for its neuroprotective properties relating to protecting dopaminergic neurons from cell death e.g. as resulting from Parkinson's disease.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

Thus, the specification discloses only limited examples that are neither representative of the claimed genus of compounds; nor does the disclosure of a handful of specific peptides comprising core peptide motifs and the in vitro receptor binding of related peptides represent a substantial portion of the claimed genus Accordingly, the undue breadth of possible "biologically active" GPE mimics/analogs/prodrugs; the unpredictable effects on bioactivity of subtle changes to the chemical structure and the stereospecificity necessary for receptor/ligand binding, the lack of guidance presented in the specification, the lack of representative examples for both making and use, necessitate the illustration of further examples demonstrating the making and use of a representative sample of peptide (or non-peptide) compounds along with a showing which is reasonably predictive and commensurate of *in vivo* utility in order to provide the requisite enablement for the presently claimed invention as broadly claimed.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-7 are rejected under 35 U.S.C. 102(a,b) as being anticipated by Gluckman, WO 93/02695 (2/93).

Gluckman teaches administering IGF-1 (an analog/mimetic of GPE as taught in the present specification pages 9-10) and analogues thereof to treat CNS injuries which are as "a

consequence of Parkinson's disease" by "direct administration (e.g. shunt). The disclosure of "Functional symptoms" (e.g. hypoxia/ischemia/trauma/demylenation" of Gluckman are within the scope of "functional symptoms of Parkinsons disease" as presently (and broadly) claimed. See e.g. Gluckman Abstract; claims etc.

10. Claims 1-7 are rejected under 35 U.S.C. 102(a,e) as being anticipated by Gluckman et al., US Pat. No. 6,187,906 (2/2001: filed 6/99 or earlier).

Gluckman et al. disclose and claim a method of protecting (e.g. treatment/prophylaxis) dopaminergic neurons (against cell death e.g. functional symptoms of Parkinson's i.e. involving dopaminergic neurons) by administering (e.g. directly to the brain): gly-pro-glu (GPE) . See abstract; examples; patent claims.

11. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noble et al. US Pat. No. 5,762,922 (6/98).

Noble et al. teach the treatment of diseases or conditions characterized by an insufficiency of a particular cell type (E.g. brain) by administration (e.g. including direct administration: e.g. see col. 7-8) of growth factors (including IGF-1) wherein the disease state is Parkinsons. E.g. see patent claim 1; patent claim 4 directed to Parkinson's. The selection of growth factors (or IGF-1) (e.g. which qualify as analogues/mimics of GPE) which treat Parkinsons would have been prima facie obvious to one of ordinary skill in the art since the selection of such growth factors and parkinson's represent preferred embodiments as evidenced by the patent claims.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No.6,187,906 (2/2001) . Although the conflicting claims are not identical, they are not patentably distinct from each other because Gluckman et al. claim a method of protecting (e.g. treatment/prophylaxis) dopaminergic neurons (against cell death e.g. functional symptoms of Parkinson's i.e. involving dopaminergic neurons) by administering (e.g. directly to the brain): gly-pro-glu (GPE) .

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)
April 7, 2003

BENNETT CELSA
PRIMARY EXAMINER